A role for von Hippel-Lindau protein in pancreatic beta-cell function.

Journal: Diabetes

Publication Year: 2009

Authors: Sapna Puri, David A Cano, Matthias Hebrok

PubMed link: 19033400

Funding Grants: Training Grant I

Public Summary:

Scientific Abstract:
OBJECTIVE: The Vhlh gene codes for the von Hippel-Lindau protein (VHL), a tumor suppressor that is a key player in the cellular response to oxygen sensing. In humans, a germline mutation in the VHL gene leads to the von Hippel-Lindau disease, a familial syndrome characterized by benign and malignant tumors of the kidney, central nervous system, and pancreas. RESEARCH DESIGN AND METHODS: We use Cre-lox recombination to eliminate Vhlh in adult mouse pancreatic beta-cells. Morphology of mutant islets is assessed by immunofluorescence analysis. To determine the functional state of Vhlh(-/-) islets, insulin secretion is measured in vivo and in vitro, and quantitative PCR is used to identify changes in gene expression. RESULTS: Loss of VHL in beta-cells leads to a severe glucose-intolerant phenotype in adult animals. Although VHL is not required for beta-cell specification and development, it is critical for beta-cell function. Insulin production is normal in beta-cells lacking VHL; however, insulin secretion in the presence of high concentrations of glucose is impaired. Furthermore, the loss of VHL leads to dysregulation of glycolytic enzymes, pointing to a perturbation of the intracellular energy homeostasis. CONCLUSIONS: We show that loss of VHL in beta-cells leads to defects in glucose homeostasis, indicating an important and previously unappreciated role for VHL in beta-cell function. We believe that the beta-cell-specific Vhlh-deficient mice might be a useful tool as a "genetic hypoxia" model, to unravel the possible link between hypoxia signaling and impairment of beta-cell function.